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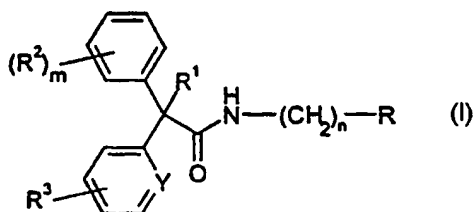
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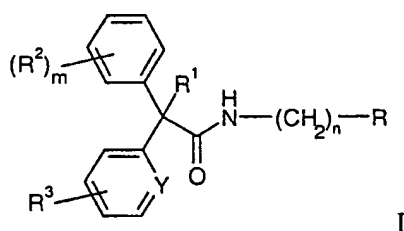
(54) Title: USE OF CARBONYLAMINO DERIVATIVES AGAINST CNS DISORDERS



(57) Abstract: The present invention is concerned with the use of carbonylamino derivatives of general formula (I) wherein R signifies lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, lower alkoxy or CF<sub>3</sub>; R<sup>1</sup> signifies hydrogen or lower alkyl; R<sup>2</sup> and R<sup>3</sup> signify, independently from each other, hydrogen, halogen or nitro; Y signifies CH or N; n is 0-6; m is 0-2; as well as with their pharmaceutically acceptable salts for the treatment of diseases, which relate to metabotropic glutamate receptor antagonists and/or agonists.

## USE OF CARBONYLAMINO DERIVATIVES AGAINST CNS DISORDERS

The present invention is concerned with the use of carbonylamino derivatives of the general formula



wherein

5 R signifies lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, lower alkoxy or CF<sub>3</sub>;

R<sup>1</sup> signifies hydrogen or lower alkyl;

R<sup>2</sup> and R<sup>3</sup> signify, independently from each other, hydrogen, halogen or nitro;

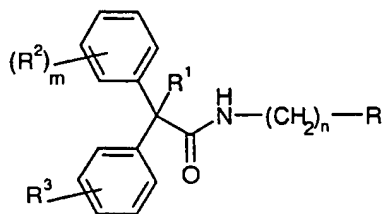
Y signifies CH or N;

n is 0 – 6;

10 m is 0 – 2;

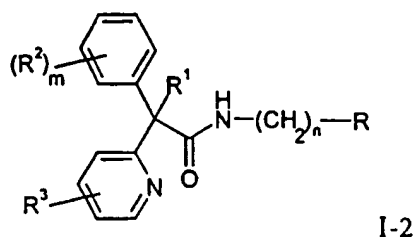
as well as with their pharmaceutically acceptable salts.

Encompassed from the present formula I are the following chemical structures:



and

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wherein the substituents  $R^1 - R^3$ , R and n and m are given above.

These compounds and their salts are known compounds and they are described per se or with similar structures in the following documents:

- 5 WO 9728005; J. Org. Chem., 62(8), 2594, (1997); Tetrahedron Letters, 38(12), 2113, 1997; EP 0 474 589; J. Med. Chem., 32(10), 2318, (1989) and US 3,534,041.

The use as mentioned below is not described in these documents.

It has now surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists and/or agonists.

- 10 In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

- L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-  
15 controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

- At present, eight different members of these mGluRs' are known and of these some even have sub-types. On the basis of structural parameters, the different second messenger signalling pathways and the different affinity to low-molecular weight chemical  
20 compounds, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as

psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord  
5 injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary  
10 incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depression.

Objects of the present invention are the use of compounds of formula I and their pharmaceutically acceptable salts in the treatment or prophylaxis of diseases, caused by activation of metabotropic glutamate receptors ligands, medicaments, containing a  
15 compound of formula I or a pharmaceutically acceptable acid addition salt thereof, and the use of compounds of formula I for the manufacture of corresponding medicaments.

Preferred compounds of formula I-1 in the scope of the present invention are those, in which Y is CH.

The following are examples of such compounds:

20 N-pentyl-2,2-diphenyl-acetamide,  
N-hexyl-2,2-diphenyl-acetamide,  
N-cyclopropylmethyl-2,2-diphenyl-acetamide and  
N-hex-2-enyl-2,2-diphenyl-acetamide.

Further preferred are compounds of formula I, wherein Y is N, for example the following  
25 compounds:

(RS)-N-cyclopropylmethyl-2-phenyl-2-pyridin-2-yl-acetamide,  
(RS)-2-(3,4-difluoro-phenyl)-N-hexyl-2-pyridin-2-yl-acetamide and  
(RS)-N-hexyl-2-(4-nitrophenyl)-2-pyridin-3-yl-acetamide.

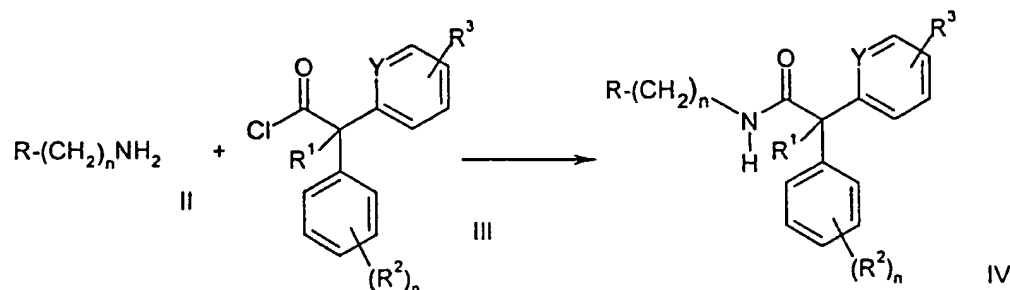
The invention embraces all stereoisomeric forms in addition to the racemates.

30 The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1 – 7 carbon atoms, preferably with 1 – 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

The term "lower alkoxy" denotes a lower alkyl residue in the sense of the foregoing definition bonded via an oxygen atom.

The term "halogen" embraces fluorine, chlorine, bromine and iodine.

The compounds of general formula I and their pharmaceutically acceptable salts can  
5 be manufactured by processes, known in the art, for example by the following scheme:



The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic  
10 acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or  
15 the like, basic amines or basic amino acids are suitable for the formation or pharmaceutically acceptable salts of acidic compounds.

The scheme gives an overview of the manufacture of the compounds of formula I starting from known compounds. The manufacture of representative compounds of formula I is described in detail in examples 1-28.

20 The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor agonists and/or antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as acute and chronic pain. Other treatable indications are  
25 restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Alzheimer's disease, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism

or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

- 5           The compounds of the present invention are group I mGlu receptor agonists and/or antagonists. It has been found that compounds of examples 1, 2, 5, 7-10, 12-21, 23, 24 and 28 are agonists. The remaining compounds have been identified as being antagonists. The compounds show activities, as measured in the assay described below.

- 10           The compounds of the present invention are group 1 mGlu receptor agonists and/or antagonists. The compounds show activities, as measured in the assay described below, of 50  $\mu$ M or less, typically 1  $\mu$ M or less, and ideally of 0.5  $\mu$ M or less.

Compounds of examples 3, 4, 6, 11, 22, 25, 26 and 27 show an antagonistic activity, the remaining compounds are agonists on the group 1 mGluR.

The following EC<sub>50</sub> values hve been measured:

Example	EC <sub>50</sub> ( $\mu$ M)
2	2.12
3	12.7
4	1.0
7	17.0
19	2.98
21	3.13
26	15.0

15

#### Test Method

- 20           cDNA encoding for rat mGlu1a receptor obtained from Prof. S. Nakanishi (Kyoto, Japan) was transiently transfected into EBNA cells using a procedure described by E.-J. Schlaeger and K. Christensen ("Transient gene expression in mammalian cells grown in serum-free suspension culture," Cytotechnology, 15: 1-13, 1998).

[Ca<sup>2+</sup>]<sub>i</sub> measurement were performed on mGlu1a transfected EBNA cells after incubation of the cells with Fluo-3 AM (0.5 μM final concentration) for 1 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES).

- [Ca<sup>2+</sup>]<sub>i</sub> measurement were done using a fluorometric imaging plate reader (FLIPR,  
5 Molecular Devices Corporation, La Jolla, CA, USA). When compounds were evaluated as antagonists they were tested against 10 μM glutamate as agonist.

The inhibition (antagonists) or activation (agonists) curves were fitted with a four parameter logistic equation giving EC<sub>50</sub>, IC<sub>50</sub> and Hill coefficient using the iterative non linear curve fitting software Origin (Microcal Software Inc., Northampton, MA, USA).

- 10 The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g.  
15 in the form of injection solutions.

- The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets,  
20 dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as  
25 alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

- In addition, the pharmaceutical preparations can contain preservatives, solubilizers,  
30 stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an

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object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert  
5 carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being  
10 weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.



## Example 1

N-Pentyl-2,2-diphenyl-acetamide

To a cooled (0°C) solution diphenylacetyl chloride (1.73 mmol) and pyridine (0.28 ml, 3.46 mmol) in dichloromethane (12 ml) was added pentylamine (0.39 ml, 2.60 mmol) and the reaction mixture was stirred at RT for 16 h. Aqueous work up and crystallization from ethyl acetate / hexane yielded the product as a light yellow solid, m.p. 101°C and MS: m/e = 281 (M<sup>+</sup>)

## Example 2

10 2,2-Diphenyl-N-propyl-acetamide

The title compound, light yellow solid, m.p. 90°C and MS: m/e = 254 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and propylamine.

## Example 3

15 2,2-Diphenyl-N-propyl-propionamide

The title compound, white solid, m.p. 62°C and MS: m/e = 267 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from 2,2-diphenylpropionyl chloride and propylamine.

## Example 4

20 N-Pentyl-2,2-diphenyl-propionamide

The title compound, colorless oil, MS: m/e = 295 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from 2,2-diphenylpropionyl chloride and pentylamine.

## Example 5

N-Butyl-2,2-diphenyl-acetamide

25 The title compound, white solid, m.p. 96°C and MS: m/e = 268.4 (M+H<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and butylamine.

## Example 6

N-Butyl-2,2-diphenyl-propionamide

The title compound, colorless oil, MS:  $m/e = 282.2$  ( $M+H^+$ ) was prepared in accordance with the general method of example 1 from 2,2-diphenylpropionyl chloride and butylamine.

#### Example 7

5 N-Cyclopropyl-2,2-diphenyl-acetamide

The title compound, white solid, m.p.  $292^{\circ}\text{C}$  and MS:  $m/e = 251$  ( $M^+$ ) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and cyclopropylamine.

#### Example 8

10 N-Heptyl-2,2-diphenyl-acetamide

The title compound, white solid, m.p.  $90^{\circ}\text{C}$  and MS:  $m/e = 309$  ( $M^+$ ) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and heptylamine.

#### Example 9

15 N-Hexyl-2,2-diphenyl-acetamide

The title compound, off-white solid, m.p.  $100^{\circ}\text{C}$  and MS:  $m/e = 296.4$  ( $M+H^+$ ) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and hexylamine.

#### Example 10

20 N-Cyclopropylmethyl-2,2-diphenyl-acetamide

The title compound, white solid, m.p.  $130^{\circ}\text{C}$  and MS:  $m/e = 265$  ( $M^+$ ) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and cyclopropylmethylamine.

#### Example 11

25 N-Cyclopropylmethyl-2,2-diphenyl-propionamide

The title compound, white solid, m.p.  $38^{\circ}\text{C}$  and MS:  $m/e = 279$  ( $M^+$ ) was prepared in accordance with the general method of example 1 from 2,2-diphenylpropionyl chloride and cyclopropylmethyl-amine.

#### Example 12

30 N-Ethyl-2,2-diphenyl-acetamide

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The title compound, off-white solid, m.p. 87°C and MS: m/e = 239 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and ethylamine.

#### Example 13

5 N-Allyl-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 186°C and MS: m/e = 251 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and allylamine.

#### Example 14

10 2,2-Diphenyl-N-prop-2-ynyl-acetamide

The title compound, white solid, m.p. 131°C and MS: m/e = 249 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and prop-2-ynylamine.

#### Example 15

15 N-(3-Methyl-butyl)-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 128°C and MS: m/e = 281 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and 3-methyl-butylamine.

#### Example 16

20 N-Hex-2-enyl-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 81°C and MS: m/e = 293 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and hex-2-enylamine.

#### Example 17

25 N-Hex-4-enyl-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 85°C and MS: m/e = 293 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and hex-4-enylamine.

#### Example 18

30 N-(5-Methoxy-pentyl)-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 74.2-75.0°C and MS: m/e = 312 (M+H<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and 5-methoxy-pentylamine.

#### Example 19

5 N-(4-Methoxy-butyl)-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 75.5-76.8°C and MS: m/e = 298 (M+H<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and 4-methoxy-butylamine.

#### Example 20

10 N-(2-Ethoxy-ethyl)-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 83.5-86.2°C and MS: m/e = 283 (M+H<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and 2-ethoxy-ethylamine.

#### Example 21

15 2,2-Diphenyl-N-(2-propoxy-ethyl)-acetamide

The title compound, white solid, m.p. 77.8-78.9°C and MS: m/e = 297 (M<sup>+</sup>) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and 2-propoxy-ethylamine

#### Example 22

20 (RS)-N-Cyclopropylmethyl-2-phenyl-2-pyridin-2-yl-acetamide

a) To a solution of (RS)-phenyl-pyridin-2-yl-acetic acid methyl ester (0.051 g, 0.22 mmol) in 3 ml of aminomethyl cyclopropane was added 4 mg (0.02 mmol) of anhydrous p-toluenesulfonic acid and the reaction mixture was heated to 83°C (reflux) for 16 h. Aqueous work up with ethyl acetate/water and evaporation of the solvents in vacuo  
25 yielded the product (0.040 g, 66%) as an orange oil, MS: m/e = 295 (M<sup>+</sup>).

The starting material (RS)-phenyl-pyridin-2-yl-acetic acid methyl ester was obtained as follows:

b) To a solution of benzyl cyanide (5.00g, 42.7 mmol) and 2-chloropyridine (4.85 g, 42.7 mmol) in 15 ml of toluene was added finely powdered sodium amide (3.33 g, 85.4 mmol)  
30 in portions keeping the temperature between 20-30°C. The suspension was refluxed for 6h. After cooling, 100 ml water is added and the product is worked up with ethyl acetate/water. After drying (MgSO<sub>4</sub>) and concentration, the crude material is purified by flash

chromatography on silicagel using a 1:4 mixture of ethyl acetate and hexane as eluant to yield 3.40 g (17.5 mmol, 41%) of (RS)-phenyl-pyridin-2-yl-acetonitrile as a white solid, m.p. 89°C and MS: m/e = 194 ( $M^+$ ).

5 c) A solution of (RS)-phenyl-pyridin-2-yl-acetonitrile (0.928 g, 4.80 mmol) in 5 ml of conc. sulfuric acid was stirred overnight at room temperature. The mixture is poured on 100 g of ice, the pH is adjusted to 8-9 by addition of 28% sodium hydroxide solution and the product is extracted with ethyl acetate/water. After drying ( $MgSO_4$ ) and concentration, the crude material is purified by flash chromatography on silicagel using ethyl acetate as eluant to yield 0.878 g (4.14 mmol, 86%) of (RS)-phenyl-pyridin-2-yl-acetamide as a white  
10 solid, m.p. 134°C and MS: m/e = 213.2 ( $M+H^+$ ).

d) (RS)-Phenyl-pyridin-2-yl-acetamide (0.340 g, 1.60 mmol) was dissolved in 5 ml of a saturated solution of HCl/methanol and refluxed for 6h in a closed vessel. The mixture is poured on 25 g of ice, the pH is adjusted to 8-9 by cautious addition of 28% sodium hydroxide solution keeping the temperature below 10°C and the product is extracted with  
15 ethyl acetate/water. After drying ( $MgSO_4$ ) and concentration, the crude material is purified by flash chromatography on silicagel using 1:4 mixture of ethyl acetate and hexane as eluant to yield 0.204 g (0.939 mmol, 59%) of (RS)-phenyl-pyridin-2-yl-acetic acid methyl ester as a white solid, m.p. 74°C and MS: m/e = 228.2 ( $M+H^+$ ).

### Example 23

20 (RS)-2-(3,4-Difluoro-phenyl)-N-hexyl-2-pyridin-2-yl-acetamide

The title compound, amorphous, MS: m/e = 333.3 ( $M+H^+$ ) was prepared in accordance with the general method of example 22(a) from (RS)-2-(3,4-difluoro-phenyl)-2-pyridin-2-yl-acetic acid methyl ester and hexylamine.

The starting material (RS)-2-(3,4-difluoro-phenyl)-2-pyridin-2-yl-acetic acid methyl ester  
25 was prepared in accordance with the general methods described in example 22(b-d) whereby (3,4-difluorophenyl)-acetonitrile instead of phenylacetonitrile was used.

One obtains impure (RS)-(3,4-difluoro-phenyl)-pyridin-2-yl-acetonitrile as a red viscous oil, MS: m/e = 230 ( $M^+$ ), which was directly used in the next step.

(RS)-(3,4-Difluoro-phenyl)-pyridin-2-yl-acetamide was obtained as a white solid, m.p.  
30 123-124°C, MS: m/e = 248 ( $M^+$ ).

One obtains (RS)-(3,4-difluoro-phenyl)-pyridin-2-yl-acetic acid methyl ester as a white solid, MS: m/e = 248 ( $M^+$ ).

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## Example 24

(RS)-N-Hexyl-2-(4-nitrophenyl)-2-pyridin-3-yl-acetamide

The title compound, yellow viscous oil, MS:  $m/e = 341$  ( $M^+$ ) was prepared in accordance with the general method of example 22(a) from (RS)-2-(4-nitrophenyl)-2-pyridin-2-yl-acetic acid methyl ester and hexylamine.

The starting material (RS)-2-(4-nitrophenyl)-2-pyridin-2-yl-acetic acid methyl ester was prepared in accordance with the general methods described in example 22(b-d) whereby (4-nitro-phenyl)-acetonitrile instead of phenylacetonitrile was used.

(RS)-(4-nitrophenyl)-pyridin-2-yl-acetonitrile was obtained as a dark red solid, m.p. 97-99°C, MS:  $m/e = 239$  ( $M^+$ ).

One obtains (RS)-(4-nitrophenyl)-pyridin-2-yl-acetamide as a beige solid, m.p. 155-156°C, MS:  $m/e = 257$  ( $M^+$ ).

One obtains (RS)-(4-nitrophenyl)-pyridin-2-yl-acetic acid methyl ester as a red viscous oil, MS:  $m/e = 273.2$  ( $M+H^+$ ).

## Example 25

N-Cyclobutylmethyl-2,2-diphenyl-propionamide

The title compound, white solid, m.p. 79°C and MS:  $m/e = 294.4$  ( $M+H^+$ ) was prepared in accordance with the general method of example 1 from 2,2-diphenylpropionyl chloride and cyclobutylmethyl-amine.

## Example 26

2,2-Diphenyl-N-(4,4,4-trifluoro-butyl)-acetamide

The title compound, white solid, m.p. 166°C and MS:  $m/e = 321$  ( $M^+$ ) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and 4,4,4-trifluoro-butylamine.

## Example 27

2,2-Diphenyl-N-(4,4,4-trifluoro-butyl)-propionamide

The title compound, white solid, m.p. 82°C and MS:  $m/e = 336.2$  ( $M+H^+$ ) was prepared in accordance with the general method of example 1 from 2,2-diphenylpropionyl chloride and 4,4,4-trifluorobutyl-amine.

## Example 28

N-Pent-4-ynyl-2,2-diphenyl-acetamide

The title compound, white solid, m.p. 90°C and MS:  $m/e = 278.2$  ( $M+H^+$ ) was prepared in accordance with the general method of example 1 from diphenylacetyl chloride and pent-4-ynyl-amine.

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Example A

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
5 Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
10 Magnesium stearate	<u>2</u>
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

15

	<u>mg/Tablet</u>
Active ingredient	200
Powdered. lactose	100
White corn starch	64
20 Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	<u>4</u>
Tablet weight	400



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Example C

Capsules of the following composition are produced:

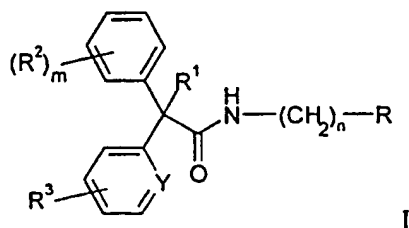
	<u>mg/Capsule</u>
5 Active ingredient	50
Crystalline lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	<u>1</u>
10 Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard  
15 gelatine capsules of suitable size.

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Claims

## 1. The use of a compound of the general formula



wherein

5 R signifies lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, lower alkoxy or CF<sub>3</sub>;

R<sup>1</sup> signifies hydrogen or lower alkyl;

R<sup>2</sup> and R<sup>3</sup> signify, independently from each other, hydrogen, halogen or nitro;

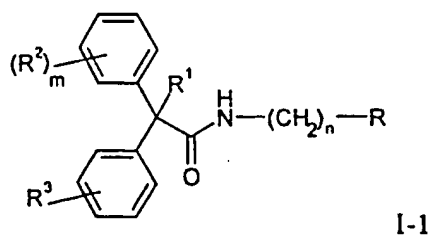
Y signifies CH or N;

n is 0 – 6 and

10 m is 0 – 2

as well as their pharmaceutically acceptable salts for the manufacture of medicaments, containing one or more compounds of formula I for the treatment of diseases, which represent therapeutic indications for metabotropic glutamate receptor ligands.

## 2. The use of a compound of formula

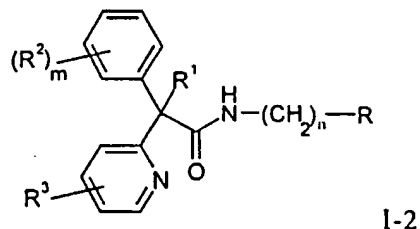


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in accordance with claim 1,  
wherein R, R<sup>1</sup> – R<sup>3</sup> and n and m have the significance given in claim 1.

3. The use of a compound of formula I-1 in accordance with claim 2, which is  
N-pentyl-2,2-diphenyl-acetamide,  
5 N-hexyl-2,2-diphenyl-acetamide,  
N-cyclopropylmethyl-2,2-diphenyl-acetamide and  
N-hex-2-enyl-2,2-diphenyl-acetamide.

4. The use of a compound of formula



- 10 in accordance with claim 1,  
wherein R, R<sup>1</sup> – R<sup>3</sup> and n and m have the significance given in claim 1.

5. The use of a compound of formula I-2 in accordance with claim 4, which is  
(RS)-N-cyclopropylmethyl-2-phenyl-2-pyridin-2-yl-acetamide,  
(RS)-2-(3,4-difluoro-phenyl)-N-hexyl-2-pyridin-2-yl-acetamide and  
15 (RS)-N-hexyl-2-(4-nitrophenyl)-2-pyridin-3-yl-acetamide.

6. A medicament containing one or more compounds of formula I in accordance with any one of claims 1 – 5 or a pharmaceutically acceptable salt thereof and an inert carrier for therapeutic indications which are concerned with group 1 mGlu receptor ligands.
- 20 7. A medicament according to claim 6, which include the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain, restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest  
25 and hypoglycaemia, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia

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caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depression.

- 5 8. The invention as hereinbefore described.

# INTERNATIONAL SEARCH REPORT

Internati Application No

PCT/EP 00/09781

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C233/11 C07C233/22 C07D213/56 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 29657 A (VANWAGENEN BRADFORD C ; SMITH DARYL (US); ARTMAN LINDA D (US); MUEL) 17 June 1999 (1999-06-17) Abstract; pages 3, 4, 46-47; claims 1-6	1, 2, 4, 6, 7
Y	the whole document	1-7
Y	WO 97 46511 A (VANWAGENEN BRADFORD C ; DELMAR ERIC G (US); MOE SCOTT T (US); SMITH) 11 December 1997 (1997-12-11) abstract; claim 1	1-7
Y	WO 96 40097 A (NPS PHARMA INC) 19 December 1996 (1996-12-19) abstract; claim 1	1-7



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

11 December 2000

Date of mailing of the international search report

18/12/2000

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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 8

The subject-matter of claim 8 is unclear and superfluous

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

In. .nation on patent family members

Internat Application No

PCT/EP 00/09781

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